CC/MIN/2020/01

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Minutes of the meeting held at 10.30am on Thursday 12th March 2020 at Public Health England, Centre for Radiation, Chemical and Environmental Hazards, Harwell Campus, Didcot, Oxon, OX11 0RQ.

Present

Chair:	Professor D Harrison	
Members:	Mr D Bodey	
	Dr G Clare	
	Dr M Cush	
	Dr R Dempsey	
	Dr J Doe	
	Dr R Haworth	
	Dr D Lovell	
	Professor N Pearce	
	Dr L Rushton	
	Dr L Stanley	
	Dr R Waring	
	Professor H Wallace	
Secretariat:	Miss B Gadeberg	PHE Scientific Secretary
	Ms C Mulholland	FSA
Assessors:	Dr H McGarry	HSE by teleconference
	Mr N O'Brien	VMD
Officials:	Professor T Gant	PHE (Items 4-5)
	Professor J O'Brien	FSA Science Council
Invited Experts and Contractors:	Dr R Bevan	IEH Consulting
	Dr P Rumsby	IEH Consulting
Observers:	Professor L Levy	IEH Consulting

ITEM 1: Announcements and apologies for absence

1. The Chair welcomed Members, and other attendees to the meeting. Apologies were received from Members: Dr R Kemp, and Assessors and Officials: Dr O Sepai (PHE), Dr J McElhiney (FSS), Dr C Ramsay (HPS), Dr H Stemplewski (MHRA), and Mr L Johnstone (BEIS).

2. The four vacancies on the Committee had been filled since the last meeting; the new Members were Dr M Cush, Dr R Dempsey, Dr R Haworth (previously co-opted Member) and Dr L Stanley. A roundtable of introductions was undertaken. Professor J O'Brien described his role as FSA Science Council observer for COM, COT and COC

3. This was Dr Rosemary Waring's last meeting. She was thanked for all her contributions to the Committee since she was appointed in 2013.

4. The annual appraisals for Members had been circulated for Members and the Chair to complete and return to the Secretariat, in time for the deadline at the end of May 2020.

5. Members were reminded to declare any interests they may have in an item before its discussion.

ITEM 2: Minutes of meeting held on 7th November 2019 (CC/MIN/2019/03)

6. Minor amendments were suggested for the draft minutes.

ITEM 3: Matters arising

Item 2 – Minutes of the meeting of 16th July 2019

7. The minutes of Item 4 of these minutes had not been circulated. It was anticipated that they would be available after the present meeting.

Item 3 Matters Arising – Scoping paper on the synthesis and integration of epidemiological and toxicological evidence in risk assessments

8. The subgroup on synthesis and integration of epidemiological and toxicological evidence in risk assessments had met by teleconference on 19th November 2019 and face-to-face on 10th February 2020.

Item 3 Matters Arising – Development of a framework for consideration of risk due to less than lifetime exposure

9. This Guidance Statement had been approved by Chair's action and would be published on the COC website soon.

10. As COT had previously expressed an interest in this item, it had been presented at the 10th March 2020 COT meeting. Feedback had been positive and the COT would consider working through an example of an assessment to illustrate the approach.

Item 7 – Guidance statement G01 – A strategy for risk assessment of carcinogenicity

11. The amendments requested at the last meeting had been made. The document would be circulated for correspondence before being finalised by Chair's action.

Item 8 – Guidance statement G08 – Risk assessment of the effect of combined exposures to multiple chemicals on carcinogenicity

12. The amendments requested at the last meeting had been made. The document would be circulated for correspondence before being finalised by Chair's action.

Item 9 – Potential toxicological risks from electronic nicotine and non-nicotine delivery systems (E(N)NDS – e-cigarettes) – update of available data on carcinogenicity

13. The COT was informed of the COC's conclusion at the December 2019 COT meeting, and the COC opinion was incorporated in the draft COT statement on E(N)NDS.

ITEM 4: Presentation on the Microbiome – Professor Tim Gant (PHE)

14. No interests were declared for this item.

15. The microbiome had been on the COC horizon scan list and Professor Tim Gant (PHE) joined the meeting to give an overview of the area and describe some of the specific aspects of relevance to chemicals and carcinogenicity. The presentation given is attached at the end of the minutes.

16. Professor Gant explained that the microbiome represented the community of microorganisms resident on or in the human body and included bacteria, viruses and fungi. The term also encompassed the environmental microbiome however the focus of the presentation and subsequent discussions was the internal one. Sequencing methods have indicated a large diversity with the total microbiome number being around 30 trillion similar to the number of cells in the human body. The gene pool was estimated to be far larger than that of the human host. The ratio of bacterial to human cells though previously reported at more than 10:1 was considered to be 1:1[a]. The microbiome has been found on any surface of the body with a connection with the environment and in particular, where conditions favour microbial growth. Humans were thought to be born sterile and the microbiome immediately establishing after birth with initial seeding dependent the route of delivery[b]. This has

[a] Sender et al (2016) Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol. 14(8), e1002533

[b] Reid et al (2011) Microbiota restoration: natural and supplemented recovery of human microbial communities. Nat Rev Microbiol. 9:27-38

been questioned as the placenta is reported to have a microbiome though there route of delivery is clearly important in establishing the early microbiome[c,d].

17. Influences on the microbiome have been shown to be both genetic and environmental. Age was an important parameter in driving diversity of the gut microbiome, as were diet and degree of exercise. The gut microbiome provided around 70% of the energy for the gut and was particularly important for the metabolism of small molecules, including environmental chemicals. Thus, changes to the microbiome may lead to changes in host phenotype. Changes to the gut microbiome diversity may alter the types of reactions occurring both for endogenous and exogenous chemicals which may also impact on any toxicological response. Differences in toxicological response had been reported within animal strains that were housed together and commonly used for chemical testing which was attributed, at least in part, to differences in the gut microbiome. Such differences allowed metabolism prior to absorption from the gut to occur in some animals, and in others no metabolism occurred, resulting in a difference in the outcome following exposure that could not be predicted[e].

18. In terms of therapeutics and disease, treatment with antibiotics may adversely affect the microbiome and the reestablishment of the microbiome could be slow, following the end of a treatment regimen. Evidence was emerging suggesting an adverse effect of antibiotics on the microbiome having a role in disease processes particularly respiratory diseases. There was some uncertainty in the epidemiology due and more evidence was required to establish the association and in particular causality. Although the microbiome may be involved in modulating toxicity it was not generally taken into account in toxicity or carcinogenicity testing.

19. Following the presentation, clarification was sought on the robustness of the epidemiological studies presented. Some doubts were raised in respect of the reliability of the epidemiological association of antibiotics use in early life with asthma incidence as stated in 18. There were studies reaching opposite conclusions and clearly more evidence was required. An example cited was that asthma incidence is negatively correlated with a higher exposure to biodiversity early in life which is thought to pre-condition the immune system which itself could be a confounding factor in these studies. A role for the microbiome in the development of cancer was thought to be much less established at present though it was possible through its role in metabolism of exogenous molecules. An important aspect of microbiome research that was considered missing, and which might impact on its use in risk assessment, was the lack of an agreed definition of what is considered ‘normal’ in both humans and animals. Linked to this was uncertainty around the significance of the intra and inter individual variability in differences in the microbiome. How such

[c] Tamburini et al (2016) The microbiome in early life: implications for health outcomes. Nat. Med. 22(7): 713-722.
[d] Aagaard et al (2014) The placenta harbors a unique microbiome. Sci. Transl. Med. 6(237): 237ra65
[e] Coen et al (2009) Mechanistic Aspects and Novel Biomarkers of Responder and Non-Responder Phenotypes in Galactosamine-Induced Hepatitis. J. Proteome Res. 8(11), 5175–5187.

variability in the microbiome affects the establishment or development of cancer was unclear.

20. The COC recognised that the microbiome was an area of concern to the general public who were aware of its potential involvement in the underpinning of a number of diseases. It was agreed that going forward, the Committee should assess how this may impact COC guidelines and opinions. This would best be achieved by establishing a baseline of what is currently known and what further work needs to be carried out to fill critical gaps in knowledge.

ITEM 5: Scoping paper – the tumour microenvironment and its role in carcinogenicity (CC/2020/01)

21. No interests were declared for this item.

22. A short overview of the immunological and stromal cell modulations relevant to cancer risk was discussed during the COC annual Horizon Scanning in November 2019. It was agreed then that a position paper on the topic should be prepared. This scoping paper outlined various aspects of the tumour microenvironment to aid identification of the issues to be incorporated in a COC position paper.

23. The scoping paper was considered to provide a good overview of the different cells in the tumour microenvironment and how these potentially interacted with neoplastic cells at the various stages of cancer development. It was noted that many of these key events were not considered in current risk assessment methodologies, instead the two-year bioassay was an integrated reflection of all events, including those relating to the tumour microenvironment. Similarly, it was also considered that epidemiology studies measured only an endpoint, for example cancer, again reflecting the entire process and that the outcome may be dependent on the exposure scenario.

24. It was thought possible that in future, the measurement of key markers of the microenvironment could be incorporated into standard testing regimes for chemicals to afford a better understanding of cancer development. The importance of collating multiple strands of evidence, i.e. from animal, human and mechanistic studies, to be integrated into a weight of evidence assessment for the effects of chemicals was also stressed. It was recognised that to achieve this a move beyond current risk assessment paradigms may be needed.

25. It was agreed that the concept of ‘whole environment impacts on cancer’ should be stressed in the preamble and summary of the COC position paper and further changes were suggested to the scoping paper to remove any potentially speculative conclusions. The COC position paper should aim to show that COC was aware of the implications of this area, rather than being specific risk assessment guidance. It was agreed that a draft position paper would be prepared for future discussion.

ITEM 6: Guidance Statement G05: Points of departure and potency estimates – second draft revision (CC/2020/02)

26. No interests were declared for this item.

27. Since publication of the first version of COC guidance statement G05 on points of departure and potency estimates, EFSA and WHO had jointly reviewed the use of the threshold of toxicological concern (TTC) approach whilst EFSA had published new guidance on bench-mark dose (BMD) modelling and updated guidance on the use of the TTC approach. A first draft revised version of G05 including these updates was presented in November 2019. This paper presented a second draft revised version of G05 addressing comments received from the previous meeting. It had also been revised to reflect changes in the WHO updated draft of 'EHC240: Principles and methods for the risk assessment of chemicals in food - Chapter 5: Dose-Response assessment and derivation of health-based guidance values', which was undergoing public consultation (WHO, 2019).

28. There was agreement from the COC that the document should be further modified, in particular to make the opinion of COC clearer throughout. Areas where historical data could be removed to rationalise section lengths were identified. Following amendment, it was agreed that the third draft revised guidance statement would be circulated to the Committee for comment.

ITEM 7: Follow up Horizon Scanning (CC/2020/03)

29. No interests were declared for this item.

30. This paper presented the priority topics from the 2019 Horizon Scanning and an overview of ongoing work by IARC and the EU Scientific Committees.

31. The Committee were informed that the Industrial Injuries Advisory Council were looking in detail into shift work and would consider the epidemiological and mechanistic information available. The COC agreed it would be useful to be kept informed of this area.

32. A short overview of Mendelian Randomisation was presented. In conventional epidemiological studies, residual confounding and other potential biases are always of concern. Randomisation has been applied as a tool to try and minimise the impact of these in controlled trials. For observational studies an alternative approach that has been used was instrumental variable analysis, in which a fixed factor of interest is chosen that is a surrogate for exposure and is unlikely to be strongly subject to confounding. Genetic variants have been utilised as instrumental variables. Within any population, genes are almost always completely randomly distributed and identification of a gene that affects the outcome of interest won't be confounded as genes are not affected by environmental or lifestyle changes. There are still potential biases which need to be explored, but in general Mendelian randomisation, in the right circumstances, can provide unbiased estimates of causal effects. Although Mendelian Randomisation had not been applied to many cancer studies to date, there was agreement for COC to acknowledge their awareness of the tool and its potential uses.

33. A presentation was also given concerning potent non-genotoxic carcinogens to assess whether the area should be further considered by the Committee. The term ‘potent’ had been applied to define carcinogenic chemicals for which a low dose was needed over a lifetime to induce tumours or, which have a short latency to tumour induction. A number of case-studies were explored for pharmaceuticals which had led to cancer within a short period of use, including BRAF inhibitors and EZH2 inhibitors. For these examples, it had been challenging to disentangle epigenetic mechanisms and accurately predict the carcinogenic response based on knowledge of the pharmacology. Several classes of environmental chemicals were noted to modify epigenetic markers; however, it has not been determined as to whether environmentally induced epigenetic alterations were part of the causative pathways that leads to cancer. Epigenetics has been previously assessed in a joint Committee statement, and it was then unclear how it could be applied for risk assessment purposes. However, as specific examples of epigenetics impacting on human cancer had been reported since the statement was written, it was agreed that the area should be revisited by COC.

ITEM 8: Draft Annual Report 2019 (CC/2020/04)

34. No interests were declared for this item.

35. This paper presented the draft COC annual report for 2019. Members were invited to send in any amendments to the Secretariat by email.

36. It was noted that Annexes 4 (Good Practice Agreement for Scientific Advisory Committees) and 5 (Glossary of Terms) would be circulated to Members for comment on the extent to which the COC complies with the Principles of the Good Practice Agreement, and any amendments or additions to be made to the Glossary of Terms.

37. Members were reminded to update their Declarations of Interest, and Affiliations for 2019, and to keep the Secretariat updated of any changes to these through the year.

ITEM 9: Any other business

38. No other business was raised.

ITEM 10: Date of next meeting

39. The next meeting would be held on 16th July 2020, at PHE Chilton.